REMARKS

Claims 1-3, 5, 9, 12-15, and 30-31 are pending in this application and under active examination. Claims 1-2, and 5 have been amended to more particularly and distinctly claim that which Applicants regard as their invention. In particular, Claims 1 and 5 have been amended to substitute "a desired protein" with "a fibrinogen having a pre-selected A chain integrity". Support for this amendment can be found, *inter alia*, on page 10, lines 23-24 of the specification. Claim 2 has been amended to correct an antecedent basis therein and to remove the word "optionally".

The amendments to the claims do not constitute new matter as defined in 35 U.S.C. § 132. Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present application.

I. Claim Rejections Under 35 U. S. C. § 103

In the Office Action, page 2 (Paper No. 16), the Examiner rejects Claims 1-3, 5, 9, 12-15 and 30-31 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Garner *et al.* (US 5,639,940) in view of Tripodi (WO 9213495) and further in view of Vukovich *et al.* (1980) and Lord (US 6,037,457). The Examiner's basis for this rejection is the same as stated in the Office Action dated December 4, 2002.

In particular, the Examiner asserts that Garner *et al.* discloses the transgenic production of fibrinogen in milk and collection and recovery of fibrinogen from the milk using precipitation, filtration and protein chromatography. While the Examiner acknowledges that Garner *et al.* does not teach the method of precipitating fibrinogen from milk in the presence of lysine, a lysine analog, ε-aminocaproic acid, or the specific HIC chromatography, it is the Examiner's position that Tripodi, Vukovich *et al.*, and Lord cure this deficiency.

Specifically, the Examiner alleges that Tripodi discloses precipitating fibrinogen from plasma with PEG in a buffer containing ε-aminocaproic acid. The Examiner further alleges that Vukovich *et al.* teaches that fibrinogen can be highly purified using HIC and Lord teaches that recombinantly produced fibrinogen can be purified by various techniques known in the art including precipitation and HIC.

In response to Applicants' distinguishing remarks over the cited references in the Amendment and Reply dated April 4, 2003, the Examiner states that:

> "[I]t is agreed that at page 4, lines 10-27 of the instant disclosure it is asserted that PEG precipitates casein with the fibrinogen. However, at page 13, lines 18-24 of the instant disclosure, PEG is suggested to be a perfectly suitable precipitant of fibrinogen from among several precipitants disclosed. This second disclosure indicated that PEG can be used by adjusting the concentration. Hence, there is no basis for asserting that the use of PEG by Tripodi is contrary to the instantly claimed invention."

Office Action, Paper No. 16, page 2, last paragraph.

The Examiner asserts that one of ordinary skilled in the art at the time the invention was made would have been motivated to purify fibrinogen transgenically produced in milk according to Garner *et al.*, by precipitation from the milk in the presence of one or more of lysine, lysine analog, or ε-aminocaproic acid as taught by Tripodi and further processes fibrinogen through HIC chromatography as taught by Vukovich *et al.*, and Lord. Applicants respectfully traverse the Examiner's rejections for the following reasons.

Without acquiescing with the Examiner's rejection and solely to advance prosecution of this case, Applicants have amended claims 1 and 5 to recite that the protein purified from milk is a fibrinogen having a pre-selected A chain integrity.

Applicants respectfully submit that the references cited by the Examiner, either alone or in combination, does not teach or suggest the two-step method of fibrinogen purification, wherein the fibrinogen has a pre-selected A chain integrity, as claimed. Applicants respectfully submit that the two-step method of the present invention is surprisingly and unexpectedly effective in purifying milk fibrinogens, wherein one can select and control the degree of the A chain integrity of fibrinogen during purification.

Garner *et al.* discloses the transgenic production of fibrinogen. Although this reference mentions that fibrinogen is collected and recovered from milk using standard practices such as precipitation, filtration and protein chromatography, as noted by the Examiner, no specific technique for the recovery of fibrinogen having a pre-selected A chain integrity from milk is disclosed. Nowhere in Garner *et al.* is the two-step method of

purification of fibrinogen of the invention as claimed taught or suggested. Neither of the secondary references cited by the Examiner cures the deficiency of Garner *et al.* to arrive at the claimed invention.

Tripodi teaches precipitating fibrinogen from plasma using polyethylene glycol (PEG) in a buffer containing ε-aminocaproic acid. Although Tripodi uses ε-aminocaproic acid in precipitating fibrinogen from plasma, ε-aminocaproic acid is used as part of a buffer whose principal precipitant is PEG. The purification technique used in Tripodi involves precipitation with PEG followed by a second step of PEG precipitation and followed by the treatment of the precipitate with glycine. Applicants submit that the teaching of Tripodi defeats the purpose of the invention because the use of PEG causes precipitation of both casein and fibrinogen together and therefore makes it impossible to separate fibrinogen from other milk proteins. Likewise, the method is incapable of allowing for selection or control of the desired A chain integrity of fibrinogen during purification.

Applicants have unexpectedly found that ε-aminocaproic acid has superior properties in preventing degradation of milk fibrinogen. Fibrinogen is very unstable and can not be successfully precipitated in the presence of protease enzymes present in milk. *See*, the specification, *inter alia*, at page 4, lines 10-19. Also, as the biochemical composition of milk is radically different from plasma, it was highly unexpected that ε-aminocaproic acid would be useful in preventing degradation of fibrinogen during purification from milk. *See*, the specification, *inter alia,* at page 22, lines 1-12.

It is known in the art that milk contains a number of proteases that have the potential to degrade foreign proteins. Addition of inhibitors of proteolysis is a common strategy in the art to inhibit degradation of foreign proteins and to minimize proteolysis of fibrinogen in milk due to the action of milk proteases. As inhibitors of proteolysis also degrade fibrinogen, it is a major problem in the art to successfully isolate and separate fibrinogen from other proteins. The inventors of this invention have provided a solution to this problem that has an immense industrial applicability.

The method of the claimed invention allows precipitation and separation of fibrinogen with an exceptionally high A chain integrity from milk. The A chain integrity of fibrinogen isolated following the method of the invention can be pre-selected and can comprise up to 80% or 100% of the F1 fragment. See the specification, *inter alia*, at page 10, lines 21-26 and

Example 2 on page 35. The production of such fibrinogens has not been taught or suggested by the references cited against the claims of this application.

Vulkovich *et al.* teaches that fibrinogen may be highly purified using HIC. However, Vulkovich *et al.* does not teach or suggest the two-step method of protein purification of the invention. Neither does Vulkovich *et al.* teach or suggest purification of a fibrinogen with a pre-selected A chain integrity as required by currently amended claims of this application.

Lord teaches that recombinantly produced fibrinogen can be purified from serum-free medium using various techniques known in the art, those listed include precipitation or HIC (*see*, column 6, lines 36 - 52). Lord does not teach or suggest the two-step method of protein purification of the invention as claimed. Neither does Lord teach or suggest purification of a fibrinogen with a pre-selected A chain integrity as required by currently amended claims of this application.

In response to Applicants' distinguishing remarks over the cited references in the Amendment and Reply dated April 4, 2003, the Examiner contends that because the specification states the use of PEG as an agent that precipitates fibrinogen, and that PEG can be used by adjusting the concentration, there is no basis for asserting that the use of PEG by Tripodi is contrary to the instantly claimed invention.

Applicants respectfully submit, as the Examiner is no doubt aware, a rejection under section 103 requires the Examiner to determine the scope and content of the prior art, and the differences between the prior art and the claimed invention *as a whole*. The Examiner has not applied Tripodi against the claimed invention *as a whole*. It is impressible for the Examiner to pick and choose sections of Applicants' specification out of context, without considering the invention as a whole, to interpret the scope of the invention as claimed. Accordingly, this aspect of the Examiner's rejection is in error.

In particular, the rejected claims specifically require precipitation of fibrinogen from milk and separation of fibrinogen from protease enzymes contained in whey and thereby recovering a part-purified fibrinogen having a pre-selected A chain integrity. The removal or partition of fibrinogen may be simultaneous to the transfer of the protease enzyme in the whey phase, or may be performed by a two-step process, whereby the protease enzymes are transferred to the whey phase prior to the the removal or partition of the desired protein. *See*, specification, page 13.

The specification at page 13, lines 18-23, referred to by the Examiner in support of the rejection over Tripodi, refers to the use of PEG to precipiate the desired protein from milk after the transfer of protease enzymes in the whey phase. This use of PEG is not the same as the use disclosed by Tripodi. Tripodi does not use PEG to percipitate fibrinogen from milk simulatneously with the transfer of the protease enzymes into the whey phase, or after the transfer of the pretease enzymes into the whey phase has been completed. Accordingly, Tripodi does not cure the deficiency of Garner *et al.*, with respect to the claimed invention.

For all the afore-mentioned reasons, Applicants respectfully submit that the combination of Garner *et al.* with any of the secondary references, even if properly made, which is not admitted, would not teach or suggest the two-step method of protein purification of the invention as claimed. Accordingly, Applicants respectfully submit that the Examiner has failed to make a *prima facie* case of obviousness against the claims of this invention.

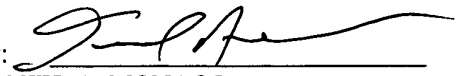
Withdrawal and reconsideration of this rejection is respectfully requested.

CONCLUSION

In light of the above, Applicants respectfully submit that all pending claims are allowable over the art of record, and a Notice of Allowance is courteously solicited. The foregoing is submitted as a full and complete response to the Office Action mailed June 18, 2003 (Paper No. 16). The Examiner is invited and encouraged to contact the undersigned attorney of record if such contact will facilitate an efficient examination and allowance of the application.

Respectfully submitted,

GRAHAM McCREATH *et al.*

By: 

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